# ANNEX 1: Comments of the EPO

# TRILATERAL PROJECT WM4 COMPARATIVE STUDIES IN NEW TECHNOLOGIES

## Comparative study on examination practice relating to single nucleotide polymorphisms (SNPs) and haplotypes

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**THE ANSWER OF THE EPO TO QUESTIONS 1-4 (EXAMPLES 1-2)**

**QUESTION 1**

**1. EXAMPLE 1**

The search for a SNP has to take into account that the single nucleotide allele of a SNP site can be defined/disclosed in different ways. Such an allele is in general defined/disclosed by either
-a gene sequence,
-a short sequence "identifier" or
-an indication of the position of the SNP site relative to a reference sequence and the nucleotide specifying the allele.
A search for a single nucleotide allele of a SNP site must therefore comprise a sequence search as well as a keyword search.
The search for allele 2 of the SNPs specified in claim 1 and 2 should therefore comprise a sequence search with the complete SEQ ID NO: 1 as well as a sequence search with oligonucleotide fragments comprising allele 2 of one specific SNP. In the present case the sequence search with the oligonucleotide fragments (~20 nt) should be done for each SNP claimed (see also answer to example 2).
The keyword search for each SNP specified in claim 1 should comprise the name(s) of the known gene in combination with the SNP position together with terms such as "variants", "mutations", "polymorphisms", etc.
The search for prior art relating to the specific use of the SNPs is considered conventional and will not be discussed further.

**2. EXAMPLE 2**

This haplotype represents a specific combination of nucleotides at SNP sites within a genomic locus found on one of an individual's chromosomes. The search for haplotypes is therefore related to the search for SNPs. A haplotype is in general defined/disclosed by either
- a gene sequence or
- an indication of the position of the SNP sites in regard to a reference sequence and the allele specifying nucleotide at each SNP site.
A search for a haplotype must therefore also comprise a sequence search as well as a keyword search.
The search for claims 1 and 2 should comprise a sequence search with at least one "SEQ ID NO: 1-haplotype". To ensure that all prior art probably disclosing the specified combination of SNPs is identified, it is also necessary to search at least some of the SNPs of the haplotypes with oligonucleotide fragments (~20 nt) comprising an allele of one specific SNP site; the extent of such a "SNP search" depends on the state of the art.
The keyword search for the haplotypes should comprise the name(s) of the known gene in combination with the specified positions of the SNPs together with a search for variants, mutations, polymorphisms, etc.
The search for prior art relating to the specific use of the haplotypes is considered conventional and will not be discussed further.

**3. Conclusions**

In regard to the search it would be of great advantage if the way SNPs and haplotypes are defined were standardized (see also answer to question 2) and if this standardized information were stored in a centralized searchable database.
A significant problem concerns the numbering of sequences. In both examples the application provides one sequence (SEQ ID NO: 1) without however providing SEQ ID NOs for the corresponding variant sequences. The positions of the SNPs are numbered relative to SEQ ID NO: 1. This may not correspond with other numbering systems which have been used in prior art documents, so that the numbered positions of the SNPs in the prior art may be different. For instance, SEQ ID NO: 1 may provide the gene sequence (including promotor regions), with numbering starting at 1; comparable sequences in the prior art may be numbered from the transcription or translation start site such that the upstream regions are numbered negatively and those downstream positively, or may use a different reference point. This need not necessarily lead to a problem in sequence searches, for instance when sequences are compared directly. It may however increase significantly the risk of missing relevant documents in a keyword search, in which the position of the SNP in the gene is used as a keyword.
In the present cases a complete search would be possible, based on the information present in and retrievable from the available databases.

**QUESTION 2**

**1. EXAMPLES 1 AND 2**

In order to determine whether or not a claimed SNP or combination of SNPs is novel, i.e. whether it was already part of the prior art before the effective date of filing of the application, it is necessary to be able to compare the content of the prior art with the claimed subject-matter. This is not always as straightforward as might be supposed. The biggest problem is one of alignment. Where several different numbering systems have been used in different documents for the same gene, direct comparison is difficult, especially if no explicit indication is provided as to the numbering system used (see also answer to question 1).

**QUESTION 3**

**1. GENERALITIES**

Under the European Patent Convention, the patent application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept (Art. 82). The assessment of the unity requirements set out in Art. 82 EPC is governed by Rule 30 EPC.
R. 30 EPC requires that for the unity requirements of Art. 82 EPC to be met the inventions to which the claims relate should be in technical relationship to each other, the relationship involving one or more of the same or corresponding special technical features, i.e. those features which define a contribution "which each of the claimed inventions considered as a whole makes over the prior art".
The boards of appeal of the EPO have consistently indicated that a lack of novelty or of inventive step of the general inventive concept underlying the application justifies a finding of lack of unity.
Therefore, when assessing whether or not an application meets the unity requirements, the first step to be taken is to identify the single general inventive concept underlying the invention(s).
The absence of this single general concept would lead to a lack of unity *a priori*.
In contrast, a lack of novelty or of inventive step of this concept will lead to an objection of lack of unity *a posteriori*.

**2. EXAMPLE 1**

**2.1 Summary**

Claim 1 relates to an isolated nucleic acid sequence comprising SEQ ID NO: 1 (which the application indicates as being a known sequence) except for a single polymorphic change, at one of 8 positions listed in the claim.
Claim 2 relates to a method for detecting disease X comprising the detection of the nucleotide present at one or more of the said 8 positions.
The description indicates that polymorphisms 1-3 are linked to disease X and it is silent as to any link of polymorphisms 7-8 with the said disease.
A clerical error in example 1 "Outline of the specification" casts some doubts on the situation with respect to polymorphisms 4-6; however, the relevant passage "...data indicating that there is no an association..." has been interpreted as meaning that there is no association between polymorphisms 4-6 and disease X.

**2.2 Unity *a priori***

The *a priori* assessment of unity is solely based on the content of the claims as interpreted in the light of the description, not taking into account either prior art documents or the general knowledge of the skilled person.
Hence, the concept linking *a priori* the 8 polymorphisms within a single invention could be represented by the fact that these polymorphisms are all to be found within SEQ ID NO: 1.
The fact that these polymorphisms belong to a specific kind of polymorphisms, i.e. that they are all single nucleotide polymorphisms (SNPs), could also provide a linking concept.
Hence, prior to any search and not taking into account any prior knowledge of the skilled person, the subject-matter of claims 1-2 would have to be regarded as meeting the unity requirements of R. 30 EPC; in other words, with respect to the subject-matter of claims 1-2 of example 1 there is unity *a priori*.
On the other hand, it should be noted that the association with disease X cannot play the role of the special technical feature required by R. 30 EPC to link all 8 polymorphic sites, because the description explicitly and unambiguously discloses that polymorphisms 4-6 are not associated with the disease and is completely silent as to any association of polymorphisms 7-8 with disease X.

**2.3 Unity *a posteriori***

The *a posteriori* assessment of unity is carried out taking into account prior art documents, obviously including those retrieved by the search, and the general knowledge of the skilled person. For the sole reason that the wording of question 3 (p. 2 of the questionnaire) requires it, the discussion on *a posteriori* unity will be split in the following two sections (discussed under 2.3.1 and 2.3.2 respectively):
1) the assessment of unity prior to carrying out the search and only taking into account the indications of the description as to what was already known, i.e. SEQ ID NO: 1, as well as the skilled person's general knowledge, and
2) the assessment of unity after having carried out the search.

**2.3.1 Unity *a posteriori* before search**

**2.3.1.a**

The information provided in the description, together with the knowledge of the skilled person with respect to SNPs, have to be taken into consideration.
As mentioned above, the description indicates that SEQ ID NO: 1 is a known sequence.
Therefore, SEQ ID NO: 1 as such cannot represent a single general inventive concept linking the 8 polymorphisms in a single invention.
(It should be noted that, if SEQ ID NO: 1 had been a novel and inventive sequence, it could have represented the single general inventive concept imparting unity to the nucleic acid

molecules to which claim 1 relates).
Moreover, the mere fact that the 8 polymorphic sites of claims 1-2 are SNPs cannot be regarded as a unifying single general inventive concept either, because SNPs as such as well as methods for their identification are very well known.
It is also well known that SNPs are to be found all over the genome and are rather frequent. Hence, the skilled person would expect to find SNPs in any given portion of the (human) genome of a sufficient length, such as a gene (from the application we know that SEQ ID NO: 1 is the sequence of a known gene).
Therefore, the feature that a group of SNPs is found within SEQ ID NO: 1 cannot, as such, represent a single general inventive concept which could link within the same invention the 8 SNPs because the skilled person would expect to find SNPs within SEQ ID NO: 1.

**2.3.1.b**

Another feature which could also be regarded as the special technical feature required by R. 30 EPC to acknowledge unity is the association of one or a group of SNPs with a particular phenotypic trait, such as the presence of a disease.
Whereas the skilled person is aware that **any** *bona fide* SNPs have a defined application, namely as genetic markers to be used, for instance, in paternity testing or for the identification of genomic loci of interest, the association of a SNP or of a group of SNPs with a specific phenotypic trait (in the present case disease X) is not an intrinsic feature of every SNP. Such a feature may or may not involve an inventive step, depending on the prior art.
If the said association is inventive, it would represent the required general inventive concept and the examining division of the EPO would acknowledge unity of invention for all SNPs **associated with the trait in question**. SNPs not associated with this trait would not belong to the same invention as those showing the association.

**2.3.1.c**

The description discloses that polymorphisms 1-3 are associated with disease X; as discussed above, this feature could represent the single general inventive concept.
Therefore, before carrying out the search, the technical problem underlying the invention can be seen in the provision of a method for detecting the presence of disease X. Polymorphisms 1-3, to which claims 1-2 relate, provide solutions to this common problem.
In view of the description, no solutions to this problem were known.
It can thus be concluded initially that polymorphisms 1-3 belong to the same invention.
On the other hand, polymorphisms 4-6 are explicitly indicated as not being associated with disease X whereas the description of the application is completely silent as to whether or not the polymorphisms 7-8 are associated with the disease.
SNPs 4-8 therefore have to be included in the category of uncharacterised SNPs, i.e. those SNPs for which no association with any trait has been shown. This kind of SNPs, only exhibiting features common to all SNPs (see item 2.3.1.a), is usually not regarded as inventive.
Polymorphisms 4-8 do not provide any solution to the aforementioned problem of providing a method for detecting the presence of disease X.
In view of this and of the fact that SNPS as well as methods for identifying them are well known, the technical problem underlying the uncharacterised SNPs 4-8, which is the same as that underlying any uncharacterised SNP, can only be seen in the provision of further SNPs. Given the absence of any concept which could link together polymorphisms 4-8 within the same invention, each of polymorphisms 4-8 represents a separate solution to this problem.

**2.1.3.d**
In view of the above, solely based on the information provided in the description that SEQ ID NO: 1 is known and on the general knowledge of the skilled person as to SNPs, it can be concluded before the search that the subject-matter of claims 1-2 lacks unity.

**2.3.2 Unity *a posteriori* after search**

The search results show that SEQ ID NO: 1 was known (as already indicated in the description of the application), whereas SNPs in SEQ ID NO: 1 were not known. The search results do not mention any method for the detection of disease X based on the detection of SNPs, such as that to which claim 2 relates.
Therefore, based on the assumption that a search with respect to such a method has been carried out and that no relevant documents have been retrieved, the technical problem underlying the invention does not change compared to the one defined prior to carrying out the search: it can be seen in the provision of a method for detecting the presence of disease X.
In view of the fact that, based on the documents retrieved by the search, no solutions whatsoever to this problem were known, let alone SNP-based detection methods for disease X, the assessment of unity reached prior to performing the search must remain the same.
It is thus concluded that polymorphisms 1-3 belong to the same invention, whereas polymorphisms 4-8 are neither linked to polymorphisms 1-3 nor to each other by a single general inventive concept as required by Art. 82 EPC.

**2.3.3 Conclusions**

The subject-matter of claims 1-2 lacks unity *a posteriori*, and relates to 6 separate inventions defined as follows:

Invention 1: Isolated nucleic acid molecules comprising SEQ ID NO: 1 except for a polymorphic change at one of the 3 positions corresponding to polymorphisms 1-3 as listed in claim 1 and methods for the detection of disease X comprising the detection within SEQ ID NO: 1 of polymorphisms 1-3.

Invention 2: An isolated nucleic acid molecule comprising SEQ ID NO: 1 except for a change at the position corresponding to polymorphism 4 as listed in claim 1 and a method for the detection of disease X comprising the detection within SEQ ID NO: 1 of polymorphism 4.

Inventions 3-6: as invention 2, wherein the polymorphisms are polymorphism 5-8 respectively.

**3. EXAMPLE 2**

**3.1 Summary**

Claim 1 relates to an isolated nucleic acid sequence comprising SEQ ID NO: 1 (which the application indicates as being the known sequence of the known gene X) except for 5 different combinations (haplotypes) of single nucleotide changes at 7 positions.
Claim 2 relates to a method for haplotyping gene X comprising the detection of the nucleotides present at each of the said 7 positions.
The description discloses that the response to drug Y of patients with disease X is better if they have haplotypes 1 or 5 than if they have haplotypes 2-4. It also discloses that haplotypes 2-4 are not associated with the disease. Although no explicit indications thereto are given in the description, from these data it can be inferred that haplotypes 1 and 5 are linked to disease X.

**3.2 Unity *a priori***

Haplotypes 1-5 are considered as having unity *a priori*, the special technical feature linking them being represented by SEQ ID NO: 1.

**3.3 Unity *a posteriori***

**3.3.1 Unity *a posteriori* before search**

The description indicates that SEQ ID NO: 1 was known: it cannot therefore provide the single general inventive concept required to acknowledge unity.

**3.3.2 Unity *a posteriori* after search**

The search results confirm that SEQ ID NO: 1 was known. They furthermore show that one haplotype characterised by the feature represented by the group of the 7 positions to which claim 1 relates was also known, namely the very haplotype 1 listed in the said claim. Therefore, this feature cannot play the role of the special technical feature linking together the subject-matter of claims 1-2 either.
In view of the fact that both SEQ ID NO: 1 and haplotype 1 were known, the claimed subject-matter is not linked together within the same invention.
On the other hand, the search results indicate that no link between any haplotypes, including haplotype 1, and disease X was known. The haplotypes for which a link to the disease has been shown, i.e. haplotypes 1 and 5, can therefore be grouped together within the same invention, whereas haplotypes 2-4 will each be considered as a separate invention.
Hence claims 1 and 2 relate to the following separate inventions:

Invention 1: Isolated nucleic acid molecules comprising SEQ ID NO: 1 with the exception that the nucleotides at positions 23, 47, 89, 213, 605, 788 and 1592 are those indicated in the table under the heading "Haplotype 1" or "Haplotype 5" and a method for haplotyping gene X comprising the determination of the identity of the nucleotides present at the said positions 23, 47, 89, 213, 605, 788 and 1592 of SEQ ID NO: 1, wherein the nucleotides are those present at these positions in haplotypes 1 or 5.
Invention 2: An isolated nucleic acid molecule comprising SEQ ID 1 except for a change at the positions 23, 47, 89, 213, 605, 788 and 1592 as indicated in the table in claim 1 under the heading "Haplotype 2" and a method for haplotyping gene X comprising the determination of the identity of the nucleotides present at the said positions 23, 47, 89, 213, 605, 788 and 1592 of SEQ ID NO: 1, wherein the nucleotides are those present at these positions in haplotype 2.

Inventions 3-4: as invention 2, wherein the haplotypes are haplotypes 3 and 4 respectively.

It should be noted that even if, for the purpose of unity, haplotypes 1 and 5 have been grouped within the same invention on the basis of their link with disease X, this feature is not part of the subject-matter of claim 1, which is a product claim. Claim 1 thus lacks novelty because haplotype 1 is known.

**QUESTION 4**

**1. EXAMPLE 1**

**1.1 Clarity**

Claim 1 relates to nucleic acid molecules defined by means of their sequences. It is therefore clear.
The same applies to claim 2, its scope being well defined. The requirements of Art. 84 EPC that claims be clear are therefore met.

**1.2 Support**

Claim 1 is a product claim and relates to nucleic acid molecules defined by their sequence. The requirement of Art. 84 EPC that claims be supported by the description are considered to be met, because the preparation of molecules such as those to which claim 1 relates is common practice for the skilled person.
However, with respect to the subject-matter of claim 2 the application lacks support (Art. 84 EPC) because no experimental data of any kind are provided showing that the presence of disease X could be detected by detecting polymorphism 4-8 and the identification of the

association between one or more SNPs and a specific trait is not a routine matter for the skilled person.
On the other hand, the application shows, by means of experimental data, that polymorphisms 1-3 are associated with disease X: therefore it provides sufficient evidence that this disease can be detected by detecting polymorphisms 1-3.
If claim 2 were restricted to a method for the detection of disease X by detecting polymorphisms 1-3 it would meet the support requirement of Art. 84 EPC.

**1.3 Inventive step**

Although inventive step is not one of the subjects to which questions 1-4 relate, a brief discussion of this issue is essential to the discussion of the industrial application of SNPs.
SNPs which are not linked to any specific trait , such as the present SNPs 4-8, are members of the group of uncharacterised SNPs.
Unless the sequence to which they belong is novel and inventive, these SNPs are usually considered as lacking an inventive step, because the gene to which they belong is known and the identification of new SNPs in a known gene only involves routine technology (see also item 2.3.1.a hereinabove).

**1.4 Industrial applicability**

A discussion as to whether the uncharacterised SNPs are susceptible of industrial application will usually not be necessary, because of their lack of inventive step.
This applies to the present polymorphisms 4-8.
In contrast, characterised SNPs, such as polymorphisms 1-3, which are linked to a specific use, will be considered as susceptible of industrial application.

**2. EXAMPLE 2**

**2.1 Clarity**

Claim 1 relates to nucleic acid molecules defined by their nucleotide sequence: the claim is therefore clear and meets the requirements of Art. 84 EPC.
The same applies to claim 2, which relates to clearly defined steps as well as to a clearly defined nucleotide sequence.

**2.2. Support**

Claim 1 meets the support requirements of Art. 84 EPC because it relates to nucleic acid sequences which can be obtained by the skilled person by routine methods.
Claim 2 relates to a method for haplotying. It is deemed to meet the support requirements of Art. 84 EPC, because the application discloses 5 specific haplotypes characterised by the very polymorphic sites to which claim 2 relates and, having been provided with these haplotypes, the skilled person would only need commomplace methods for identifying the bases at the specific positions to which claim 2 relates.

**2.3 Inventive step**

Although inventive step is not one of the subjects to which questions 1-4 relate, it can be said that the assessment of an inventive step for the subject-matter of claims 1 and 2 would probably represent the major challenge for the EPO.

**2.4 Industrial applicability**

The subject-matter of claims 1-2 is considered to be industrially applicable, and meets thus the requirements of Art. 57 EPC, because the nucleic acid sequences to which claim 1 relates can be used, for example in the method to which claim 2 relates.